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A FACILE ROUTE TO 1-ACETOXY- AND 1-METHOXYINDOLES[1]

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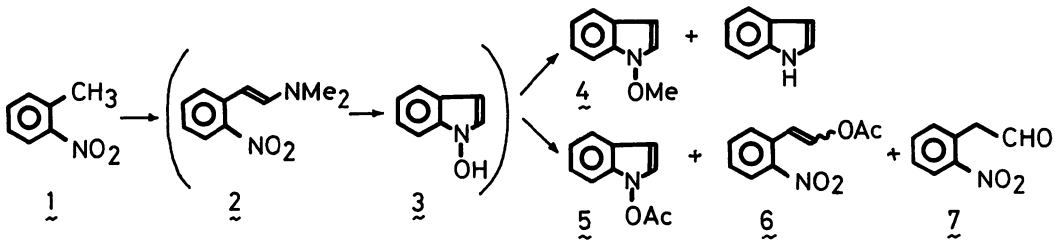
Abstract: A simple and practical synthetic method for 1-acetoxy- and 1-methoxyindoles from 2-nitrotoluene is described.

Since the isolation of 1-hydroxyindole derivatives from plants[2] and microorganisms,[3] intense efforts have been focused on their synthesis.[4] Acheson et al.[5] demonstrated that 1-hydroxyindole could be prepared by the reduction of 2-nitrophenylacetaldehyde (7) with zinc and ammonium chloride. Though subsequent treatment of 1-hydroxyindole (3) with acetic anhydride gave 1-acetoxyindole (5), its synthesis from 2-nitroaniline was troublesome in addition to poor overall yield.

Now, we wish to report a simple and practical synthetic method for 1-acetoxy- and 1-methoxyindoles from 2-nitrotoluene (1). Although all synthetic attempts of 1-hydroxyindole so far reported[4,5] used 7 as a starting material, the compound (7) is not readily available due to its unstable nature. For example, an attempt to obtain 7 directly by hydrolysis of the corresponding enamine is known to give unsatisfactory results.[4,5,6] However, recent work[7] in this laboratory for the synthesis of various 4-substituted 1-hydroxyindoles suggested that the direct reduction of the corresponding enamine with zinc and ammonium chloride, without isolation of 7, would be an attractive route for the synthesis of 1-hydroxyindole.

Thus, 2-nitrotoluene (1) was converted to the enamine (2) by the reaction with dimethylformamide dimethyl acetal (DMFDMA). The resultant enamine (2)



1 2 3 4 5 6 7

was directly reduced with zinc and ammonium chloride in ether and water in two phases. Subsequent treatment of the crude 1-hydroxyindole (3) thus obtained either by excess of methyl iodide in 10% aqueous sodium hydroxide containing phase transfer catalyst or with acetic anhydride gave 1-methoxyindole (4) or 1-acetoxyindole (5) in 62% or 61% yields, respectively.

Since the compounds (4) and (5) have now become readily available, our further efforts are focused on the synthesis of 1-hydroxyindole derivatives and their reactions.

1-Methoxyindole (4) ——— A solution of 1 (1.0 g) in abs. DMF (8 ml) and DMFDMA (1.84 g, 2 mol equiv.) was refluxed for 15.25 hr with stirring. After evaporation of the solvent in vacuo, the resultant enamine (2) was dissolved in ether (50 ml). A solution of NH_4Cl (1.43 g) in H_2O (10 ml) and zinc (9.13 g) was added and stirring was continued for 2.5 hr at room temperature. After removal of zinc by filtration through silica gel, the filtrate was washed with sat. aq. $NaHCO_3$. To the ether solution of the crude 1-hydroxyindole (3), MeI (5.45 g), 10% NaOH solution (50 ml), and tri(n-octyl)methylammonium chloride (332 mg) were added. After stirring for 20 hr at room temperature, the whole was washed with sat. aq. NaCl, dried, and concentrated to leave an oil, which was column chromatographed on silica gel with CH_2Cl_2-hexane (3:7, v/v). From the early part of the fraction, 4 (666 mg, y. 62%) was obtained. Mass and all spectral data were identical with those reported by Acheson.[5a] From the later part of the fraction, indole (61 mg, y. 7%) was obtained.

1-Acetoxyindole (5) ——— A solution of 1 (210 mg) in abs. DMF (2 ml) and DMFDMA (362 mg, 2 mol equiv.) was refluxed for 15.25 hr with stirring. After evaporation of the solvent in vacuo, the resultant enamine (2) was dissolved in ether (10 ml). A solution of NH_4Cl (290 mg) in H_2O (2 ml) and zinc (1.61 g) was added and stirring was continued for 2.5 hr at room temperature. After removal of zinc by filtration through silica gel, the filtrate was washed with sat. aq. $NaHCO_3$. To the ether solution of crude 1-hydroxyindole (3), Ac_2O (0.8 ml) was added and stirred for 16.5 hr at room temperature. The whole was washed with sat. aq. $NaHCO_3$, then with sat. aq. NaCl, dried, and evaporated to leave an oil. Column chromatography was performed on silica gel with CH_2Cl_2-hexane (1:1, v/v). From the early part of the fraction, 5 (162 mg, y. 61%) was obtained. The product was identified as 1-acetoxyindole by the comparison of mass and other spectral data with those reported by Acheson.[5a] From the middle part of the fraction, 2-nitro-β-

acetoxystyrene (6, 5 mg, y. 2%) was obtained. Its NMR spectrum showed that 6 was a mixture of cis and trans isomers. Treatment of 6 with 10% aq. HCl in MeOH afforded 7 and its dimethyl acetal in 58% and 37% yields, respectively. From the later part of the fraction, 7 (6 mg, y. 2%) was obtained.

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